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Efficacy of gabapentin as adjunctive therapy in a large, multicenter study

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The objective of this study was to determine the efficacy of gabapentin as adjunctive therapy in doses required to achieve the most effective seizure control. There were 2016 patients with partial seizures requiring adjunctive therapy who received gabapentin at doses up to 3600 mg/day in this open-label, multicenter, 16-week study.

Of the 1055 patients evaluable for efficacy, 573 received gabapentin ≤1800 mg/day and 482 received >1800 mg/day as the highest dose received. For the overall efficacy evaluable population, the percentage of patients achieving at least a 50% reduction in seizure frequency was 76.0%; 46.4% of the patients were seizure free. Patients whose highest gabapentin dose did not require >1800 mg/day had, at baseline, fewer seizures and were receiving fewer concomitant antiepileptic drugs (AEDs) at baseline than those patients requiring >1800 mg/day. This suggests that patients requiring higher doses of gabapentin were more refractory to drug treatment at the start of the study. Gabapentin was well tolerated at all doses in this study. The results of the study demonstrate that gabapentin is effective as adjunctive therapy in patients with partial seizures whose seizures are inadequately controlled by traditional AEDs.

Key words: gabapentin efficacy; epilepsy; partial seizure—human.

INTRODUCTION

The options available for antiepileptic drug (AED) therapy in the 1990s expanded to include new drugs such as gabapentin, felbamate, topiramate, lamotrigine, and tiagabine[1–4]. Monotherapy with conventional AEDs, such as phenytoin, carbamazepine, valproic acid, primidone and phenobarbital, does not provide satisfactory seizure control in 15–20% of patients with epilepsy[5], many of whom experience partial seizures. Use of conventional AEDs in combination increases the incidence of adverse events associated with these drugs, further compromising the quality of life of the patients. In addition, significant drug–drug interactions occur, which can complicate management of the patients. New drugs with better side-effect profiles and greater efficacy are clearly needed to control seizures in patients with epilepsy.

Gabapentin is a new antiepileptic agent that is structurally related to γ-aminobutyric acid (GABA). Unlike GABA, gabapentin crosses the blood–brain barrier[6,7], but despite its structural similarity with GABA, gabapentin does not appear to act through any known GABA mechanisms. Studies in rats with radiolabeled gabapentin reveal binding sites for this molecule in the neocortex and hippocampus, the function of which has yet to be determined[8,9].

Gabapentin has a good safety profile, as predicted by its lack of pharmacokinetic interactions: it is not bound to plasma proteins, is not metabolized, does not induce liver enzymes, and does not modify plasma concentrations of standard AEDs[10]. These characteristics make gabapentin especially promising as adjunctive therapy in the treatment of refractory epilepsy, and its safety and efficacy have been demonstrated in several large, placebo-controlled clinical trials[11–13].

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The present study, called STEPS (Study of Neurontin: Titration to Effectiveness and Profile of Safety), examined the effectiveness of gabapentin when used as adjunctive therapy and when titrated to doses required to achieve the most effective seizure control. This multicenter trial focused particular emphasis on obtaining effectiveness data for doses up to 3600 mg/day in epilepsy patients whose partial seizures were inadequately controlled with maximally tolerated doses of a traditional AED regimen. These doses were achieved by optimizing seizure control for each individual patient.

This post-approval study involved patients in clinical practice, rather than the more refractory and more restricted patient populations enrolled in Phase II and III clinical trials. The purpose of this study was to corroborate and expand upon the observations of controlled clinical trials, by investigating effectiveness in a heterogeneous patient population.

MATERIALS AND METHODS

Entry criteria

Patients entering this study were classified as having partial seizures with or without secondary generalization according to the Commission on Classification and Terminology of the International League Against Epilepsy[14], as determined by seizure history or appropriate findings detected by electroencephalography. To qualify, patients had to have inadequate seizure control (at least two partial onset—simple and/or complex—seizures a month when averaged over the previous 3 months) while taking one and no more than two stabilized standard AEDs. Patients were to have been taking the maximum tolerated dose or be within the recognized therapeutic serum level on at least one AED, and AED therapy was to have been stable for at least 30 days prior to entering the study. Male or female patients over 12 years of age, who were capable of compliance and were able to follow the instructions of the investigator, were eligible for this study. Female patients were not to be pregnant or nursing, and, if sexually active, female patients were to be practicing reliable methods of contraception. Patients were excluded from the study who: had demonstrated sensitivity to the drug or its ingredients; were treated with gabapentin within 30 days prior to the study; had primary generalized seizures, psychogenic seizures, or a history of non-epileptic seizures; had a history of a progressive CNS lesion or progressive encephalopathy; had severe hepatic or renal insufficiency or significant hematological disease; had taken any other experimental drugs within the 2 months prior to the trial; or who had serious or unstable medical or psychological conditions that, in the opinion of the investigator, would have compromised the patient's participation in the study. All patients or their legal guardians provided written informed consent to participate in the study.

Design

This was a multicenter, open-label, 16-week study conducted by 772 investigators in the United States and six in Canada. This study was designed to compare the safety and tolerability of gabapentin at doses of $\leq$1800 mg/day with those $>$1800 mg/day (up to a maximum of 3600 mg/day), when titrated to achieve the most effective seizure control. It was conducted in an outpatient setting with the protocol reflecting usual practice and each patient serving as his/her own control. All investigators used the same protocol, case report form, and data collection methods. This study received institutional review board approval for each site and study procedures were reviewed at a pre-study meeting.

Patients were to have six scheduled office visits and one additional visit, which could have occurred either by telephone or in the investigator's office. At the first visit (visit 1), physical and neurological examinations were performed, medical and seizure histories recorded, and a baseline quality-of-life questionnaire (QOLIE-31) was completed. The baseline seizure data was retrospective, based on patient reports of the number and type of seizures which occurred during the 3 months prior to visit 1.

Patients were to begin gabapentin therapy with 900 mg/day (titrated over a 3-day period in increments of 300 mg/day). One week after initiation of gabapentin therapy a follow-up visit was scheduled, either in the investigator's office or by telephone. It is important to note that this was not a fixed-dose study; the gabapentin dose was increased to 1800, 2400, or 3600 mg/day sequentially during the course of the study if the patient had one or more seizures at least 2 days after the previous dose increase had been reached, or if the investigator deemed it necessary. Thus, each patient's dose was determined by his/her clinical need.

At visits 2–5, seizure and safety assessments were performed and, if any seizures had occurred at least 2 days after the previous dose increase had been reached, or if the investigator deemed it necessary, the dose of gabapentin was increased to 1800 mg/day. If the patient had already reached 1800 mg/day, then the dose was increased sequentially to 2400 mg/day and then to a maximum dose of 3600 mg/day.

If a patient experienced an adverse event related to gabapentin administration, the dose could be decreased to that previously tolerated. If the patient was

receiving 1800 mg/day at the time of the adverse event, the gabapentin dose was decreased to 1200 mg/day. Once the symptoms resolved, the dose was increased at the investigator's discretion.

At visit 6, 16 weeks after gabapentin therapy began, seizure and safety assessments were completed, physical and neurological examinations performed, and the patient was to have completed a second quality-of-life questionnaire. Participation in the study ended with visit 6.

Patients recorded seizure episodes on a calendar, and the investigator reviewed these calendars at each visit and recorded the number and type of seizures that had occurred since the previous visit.

All concomitant medications were optimized prior to study entry and kept at a constant dose throughout the study. Changes were allowed, however, in order to maintain (not improve) a patient's condition. No medications were prohibited during the study, with the exception of experimental drugs.

Patients were able to withdraw from the study at any time, but every effort was made to have patients complete the study within the bounds of safety and the provisions of informed consent. Patients who withdrew from the study before completing 16 weeks of therapy had safety and seizure assessments and physical and neurological examinations performed at the time of withdrawal.

One year after patients had completed the study, investigators completed a follow-up questionnaire for patients who had continued on gabapentin treatment following the end of the 16-week study period. For each patient, the investigator recorded the daily dose of gabapentin, the dosing regimen, daily dose of concomitant AEDs, and overall assessments of seizure control and safety/tolerability of the patient's current therapy.

Main outcome measures

Efficacy was evaluated by the change in the number and percentage of total seizures, the proportion of patients who were seizure free, and by the physician's assessment of seizure control (excellent, good, fair, or poor) at study completion or dropout. In addition, the percentage change in seizure frequency and the percentage of patients who were seizure free was evaluated for each type of partial seizure.

The percentage change and absolute change from the retrospective baseline to weeks 13–16 in seizure frequency by seizure type (simple partial, complex partial, secondarily generalized tonic–clonic) and overall were determined. The absolute change from baseline was calculated as the difference in seizure frequency between weeks 13–16 and baseline. A negative change from baseline represented a decrease in seizure frequency and was considered favorable.

For each patient, the percentage change from baseline in overall seizure frequency was calculated as: $100(T - B)/B$, where T is the number of seizures reported during weeks 13–16 and B is the average number of seizures per month at baseline. The responder rate was calculated for the seizure population as the proportion of patients with a $\geq$50% reduction from baseline in partial seizure frequency during the last 4 weeks of the study (i.e. the proportion of patients for whom the percentage change from baseline in seizure frequency indicated a decrease of $\geq$50%).

The cumulative proportion of patients at or below each dose level was taken to be the number of patients who were receiving gabapentin at that or a lower dose level and had the desired outcome (i.e. seizure free or responder) divided by the total number of patients included in the analysis overall.

Seizure control analysis included all patients who completed 16 weeks of therapy, missed no more than 20% of the scheduled doses at any visit, were not treated with gabapentin for at least 3 months prior to starting the study, and had a least a 3-week duration between the final visit and the previous visit.

Statistical methods

All data processing, summarization, and analyses were performed using SAS for UNIX, Version 6.09.

Patient demographics and baseline epilepsy characteristics were summarized descriptively (i.e. mean, standard error, median, minimum, maximum for continuous parameters, frequency distributions for categorical parameters) for all patients who received at least one dose of study medication.

The percentage change and absolute change in the number of seizures from baseline to the end of study weeks 13–16 and the corresponding 95% confidence interval (for percentage change) were calculated overall, as well as for each of the seizure types (simple partial, complex partial, and secondarily generalized tonic–clonic).

The percentage of patients who were seizure free during weeks 13–16 and the corresponding 95% confidence interval were calculated overall, as well as for each of the seizure types (simple partial, complex partial, and secondarily generalized tonic–clonic).

In addition to evaluating the patients overall, analyses were also performed based on the final dose ($\leq$1800 mg/day or $>$1800 mg/day).

RESULTS

Part 1—Descriptive

There were 2216 patients entered into the study. Safety analyses were performed on data from all patients taking at least one dose of study medication and participating in at least one follow-up contact ($n = 2216$). This population was also used for the overall physician's assessment of seizure control. Efficacy analyses were performed on data from all patients who completed the study, had approximately 16 weeks of therapy, missed no more than 20% of the doses at any visit, and were not treated with gabapentin within 3 months prior to the start of the study. The above criteria were met by 1055 patients, who were therefore evaluable for efficacy: 573 received gabapentin ≤1800 mg/day and 482 received >1800 mg/day as the highest dose during the study (Fig. 1, Table 1). Patients could have reported more than one seizure type. The distribution of seizure type at baseline was similar for the two groups of patients, those who received gabapentin ≤1800 mg/day and those who received >1800 mg/day as the highest dose (Table 2).

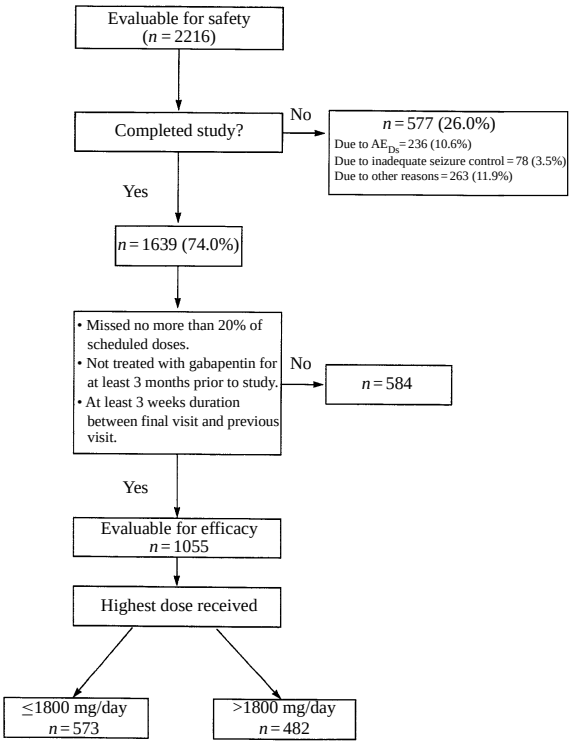

Fig. 1: Patients evaluable for efficacy analysis.

Table 1: Patient characteristics.

Characteristic	Gabapentin ≤1800 mg/day $n = 573$	Gabapentin >1800 mg/day $n = 482$	Total $n = 1055$
Age (mean year)	40	37	39
Ethnic origin			
Caucasian	459	380	839
Hispanic	43	37	80
Black	53	51	104
Asian	6	5	11
Other	10	7	17
Missing data	2	2	4
Gender			
Male	258	236	494
Female	314	246	560
Missing data	1	0	1

The baseline seizure frequency was lower for the group of patients that required less gabapentin (≤1800 mg/day) than for the group that required >1800 mg/day as the highest dose received (Table 3). Patients in the group that required doses of gabapentin ≤1800 mg/day also were taking fewer concomitant AEDs at baseline than were patients who required >1800 mg/day (Table 4).

Part 2—Outcomes

Efficacy During the last 4 weeks of the study, efficacy evaluable patients experienced an average decrease in seizures of 61.0%. During this time, 46.4% of the patients were seizure free (Table 5). The overall mean seizure frequency decreased from 17 per month at baseline to 4.5 during the last 4 weeks of the study. When the data were analysed over the last 8 weeks of the study, 634 patients were evaluable for efficacy, 47.2% of whom were seizure free, with a responder rate of 75.4%. The drop in the number of patients evaluable for the analyses over the last 8 weeks was a result of all patients not having a visit during the time window despite having completed the 16-week study.

The cumulative percentage of patients who were seizure free is presented in Fig. 2. To achieve seizure freedom, 33.4% of the total patients (352/1055) required gabapentin doses ≤1800 mg/day as their highest dose during the last 4 weeks of the study, and 46.4% of patients taking any dose up to 3600 mg/day achieved seizure freedom. The cumulative responder rate is presented in Fig. 3. Nearly half (44.9%) of patients achieved a 50% reduction in seizure frequency at gabapentin doses ≤1800 mg/day, and for all doses up to 3600 mg/day the responder rate was 76.0%.

Table 2: Seizure population: baseline seizure type.

Seizure type	Gabapentin ≤1800 mg/day $n = 573$	Gabapentin >1800 mg/day $n = 482$	Total $n = 1055$
None/unknown	64	56	120
Simple partial only	90	63	153
Complex partial only	217	200	417
SGTC only	54	37	91
Simple partial + complex partial	59	36	95
Simple partial + SGTC	22	11	33
Complex partial + SGTC	67	79	146

SGTC: secondarily generalized tonic–clonic.

Table 3: Seizure population: baseline seizure frequency.

Characteristic	Gabapentin ≤1800 mg/day $n = 573$	Gabapentin >1800 mg/day $n = 482$	Total $n = 1055$
Duration of epilepsy (mean year)	17	19	18
Baseline seizure frequency			
Mean number per month	14	20	17
Median number per month	4	7	5

Table 4: Concomitant AEDs.

Number of concomitant AEDs at baseline (number (%) of patients)	Gabapentin ≤1800 mg/day $n = 573$	Gabapentin >1800 mg/day $n = 482$	Total $n = 1055$
1	363 (63)	247 (51)	610 (58)
2	155 (27)	205 (43)	360 (34)
≥3	11 (2)	10 (2)	21 (2)
None/unknown	37 (2)	20 (4)	57 (5)

Table 5: Efficacy analysis.

	Gabapentin ≤1800 mg/day $n = 573$	Gabapentin >1800 mg/day $n = 482$	Total $n = 1055$
Average percentage decrease in seizures	71.1%	49.1%	61.0%
Percentage seizure free	61.4%	28.4%	46.4%
50% responder rate	83.2%	67.6%	76.0%

Table 6: Mean percentage decrease in seizures from baseline.

Baseline seizure type	Gabapentin ≤1800 mg/day $n = 573$	Gabapentin >1800 mg/day $n = 482$	Total $n = 1055$
Simple partial	67.0 (90)	37.8 (63)	55.0 (153)
Complex partial	65.0 (217)	43.5 (200)	54.7 (417)
SGTC	77.0 (54)	41.7 (37)	62.7 (91)
Simple partial + complex partial	81.8 (59)	59.5 (36)	73.4 (95)
Simple partial + SGTC	86.0 (22)	78.2 (11)	83.4 (33)
Complex partial + SGTC	69.5 (67)	59.7 (79)	64.2 (146)

SGTC: secondarily generalized tonic–clonic. Patients may have exhibited more than one seizure type.

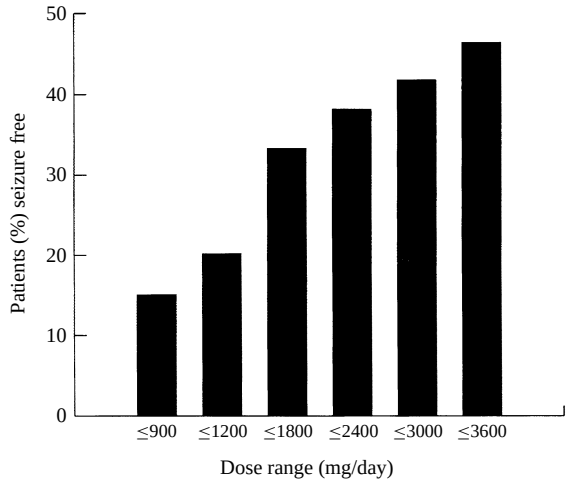

Fig. 2: Cumulative percentage of patients who were seizure free at each dose range of gabapentin.

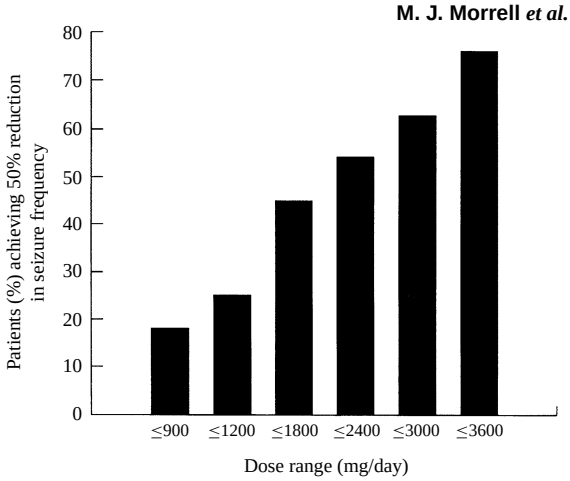

Fig. 3: Cumulative percentage responder rate at each dose range of gabapentin.

The mean percentage decrease in seizures from baseline by seizure type is presented in Table 6 and the percentage of patients who were seizure free during the last 4 weeks of the study by seizure type is presented in Table 7.

Seizure control provided by gabapentin, as assessed by the physicians at study completion or dropout, was judged to be excellent or good for 66.1% (1465/2216) of the patients.

To confirm the results of the efficacy analysis, a modified intent-to-treat analysis was performed. To be eligible for the intent-to-treat analysis, patients had a total duration while on gabapentin of $\geq$30 days, a baseline after day 20, and a final visit between days 30 and 140 with a seizure record at each visit. In addition, the last visit had to have been $\geq$14 days after the previous visit. These criteria for analysis were met by 1668 patients. For these patients, the responder rate was 74%, and 44% of the patients were seizure free. The results of this analysis were consistent with the results of the efficacy analysis for the evaluable population.

Safety The four most commonly reported adverse events in the efficacy evaluable population ($n = 1055$) were: somnolence (14.9%); dizziness (10.0%); asthenia (5.8%); and headache (4.5%). These four events were identical to the four most commonly reported events for all 2216 patients participating in the study.

Long-term follow-up Data were returned on 1095 patients for the long-term follow-up, 74.9% (819/1095) of whom were receiving gabapentin 1 year after completion of the study. The daily dose of gabapentin ranged from 300 to 6400 mg/day, with a mean daily dose of 2048 mg/day overall. The majority (86.4%; 701/811 with data) had a TID dosing regimen. At the long-term follow-up, 88.2% of those patients receiving gabapentin (723/819) were also receiving at least one other AED. The most common concomitant AEDs were carbamazepine (24.7%; 202/818 with data) and phenytoin (18.4%; 151/818 with data). The most frequently reported combination was carbamazepine and valproate (4.5%; 37/818 with data). Physicians' assessment of seizure control 1 year after the completion of the study was judged to be excellent or good for 80.6% (660/819) of the patients. Safety and tolerability was rated as excellent or good in 94.4% (773/819) of the patients.

DISCUSSION

The results of this study demonstrate that gabapentin is effective as adjunctive therapy in patients with partial epilepsy whose seizures are inadequately controlled by traditional AEDs. For individual patients, efficacy did not plateau, because the dose of gabapentin was increased in the event of a lack of complete seizure control. Rather, efficacy increased incrementally with each dose, resulting in seizure freedom in additional groups of patients. At both dose levels, $\leq$1800 mg/day and $>$1800 mg/day, a large number of patients who remained in the trial and were efficacy evaluable were seizure free during the last 4 weeks of the study.

As this was not a fixed-dose study, but rather patients were optimized to clinical response, two clearly different groups of patients emerged. One group of patients responded to lower doses ($\leq$1800 mg/day) of gabapentin and a second group

Table 7: Percentage of patients who were seizure free during the last 4 weeks of the study by seizure type.

Baseline seizure type	Gabapentin ≤1800 mg/day $n = 573$	Gabapentin >1800 mg/day $n = 482$	Total $n = 1055$
Simple partial	68.9 (90)	27.0 (63)	51.6 (153)
Complex partial	60.4 (217)	30.0 (200)	45.8 (417)
SGTC	74.1 (54)	37.8 (37)	59.3 (91)
Simple partial + complex partial	62.7 (59)	22.2 (36)	47.4 (95)
Simple partial + SGTC	40.9 (22)	54.5 (11)	45.5 (33)
Complex partial + SGTC	53.7 (67)	21.5 (79)	36.3 (146)

SGTC: secondarily generalized tonic–clonic. Patients may have exhibited more than one seizure type.

required higher doses (>1800 mg/day) to achieve a response. Analysis of the baseline characteristics of the patients according to the dose level of gabapentin demonstrated that those who required the lower dose had fewer seizures and were taking fewer AEDs at baseline than were patients who required higher doses.

The percentage of patients who were seizure free (46.4%), the responder rate (76.0%), and the average percentage decrease in seizures (61.0%) were higher in this study than in previously reported clinical trials[11–13]. One study with 113 patients evaluable for efficacy showed a responder rate of 25% for patients receiving gabapentin 1200 mg/day[11]. In another study comprising 245 patients, the responder rate was 22% for patients receiving gabapentin 900 mg/day and 27% for those receiving 1200 mg/day[13].

In a previous post-approval study, called the Neurontin Evaluation of Outcomes in Neurological Practice (NEON) Study, the effectiveness of gabapentin as adjunctive therapy was examined in 114 patients with complex partial seizures who were not controlled on existing therapy[15]. Patients in the NEON study generally had milder epilepsy than patients who are seen in tertiary care hospitals, and were generally treated by community neurologists. Patients received gabapentin 600–2400 mg/day for a 20-week period, in addition to carbamazepine and/or phenytoin. During the last 8 weeks of the NEON study, 73% of patients with all types of complex partial and/or secondarily generalized seizures had a better than 50% reduction in seizure frequency. Of those patients, 46% were seizure free. Tolerability of gabapentin was considered to be excellent or good in 76% of the patients in the NEON study, with the main adverse events being somnolence (10%), dizziness (5.4%), and asthenia (3.6%).

The higher responder rates found in the present study and the NEON study than in Phase III clinical trials could be the result of the higher doses of gabapentin used in these studies, or could reflect the real-world population of patients, who tend to be less refractory than those in Phase II and III clinical trials.

The percentage of patients for whom investigators judged seizure control to be excellent or good was highest for patients receiving ≤1800 mg/day and lowest for patients receiving >3600 mg/day, again reflecting patients whose seizures were more easily controlled at the lower doses and patients whose seizures were more difficult to control, even at higher doses. The results of this study support the practice of increasing the dose of gabapentin if the patient is still experiencing seizures at a lower dose: titrating to a higher dose provides an incremental benefit without sacrificing tolerability.

The results of the long-term follow-up revealed that nearly all (96.7%; 788/814 with data) of the patients who were receiving gabapentin 1 year after completion of the study were receiving doses ≤3600 mg/day, and most (88.2%) were receiving gabapentin and at least one other AED.

Even at the higher doses used in this study, the tolerability of gabapentin was good. The most commonly reported adverse events, somnolence, dizziness, asthenia, and headache, were reported with frequencies similar to those in studies at which gabapentin was administered in lower doses[11–13]. In addition, patients who received doses of gabapentin >1800 mg/day in this study did not experience adverse events at significantly higher rates than did those patients receiving ≤1800 mg/day[16].

Several reviews of the literature have analysed the published data on the new AEDs in order to compare the efficacy and tolerability of these drugs[17,18]. These analyses suggest that the new drugs provide valuable alternatives to standard AEDs. Gabapentin is clearly well tolerated[17], and should be considered for patients taking several drugs or with a history of drug intolerance[18].

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